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An Unusual Turn Structure in Peptides Containing α–Aminoxyacids

SUPPORTING INFORMATION

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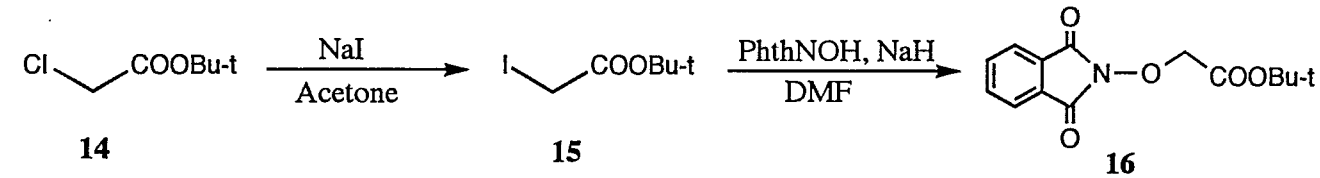
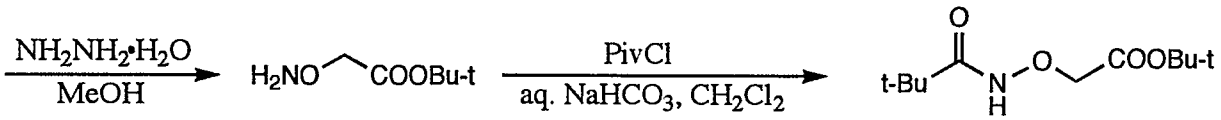
Synthesis and Characterization of Compounds 10–13

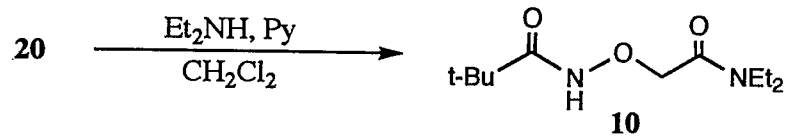


14 **15** **16**



17 **18**

19 **20**



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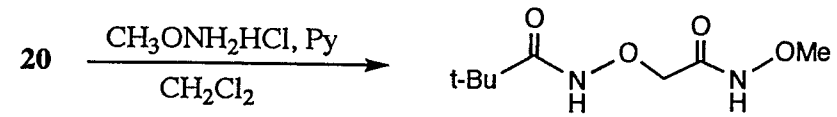

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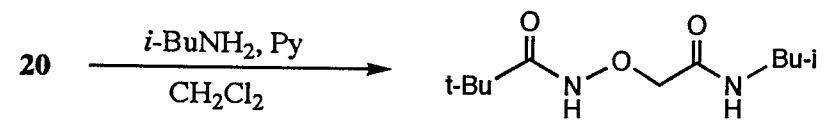

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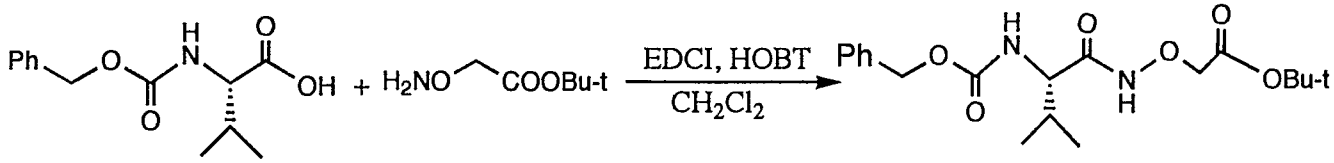
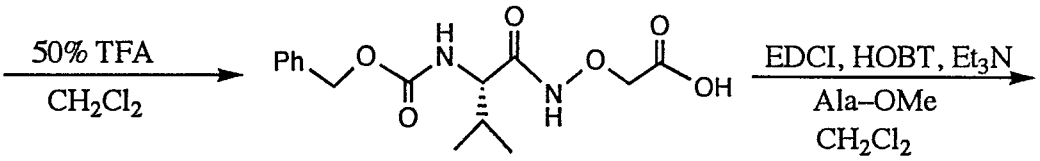


Cbz-Val **17** **21**



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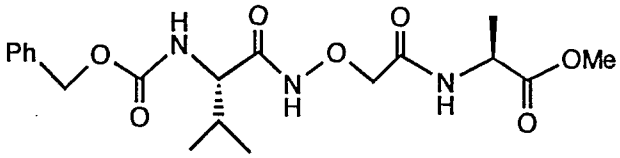

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Preparation of Compounds 15 and 16

To a solution of of sodium iodide (5.51 g, 36 mmol) in dry acetone (30 mL), compound **14** (4.61 g, 31mmol) in acetone (10 mL) was added. A precipitate of sodium chloride soon began to form. The mixture was stirred at room temperature for 30 min and then refluxed for 1 h. After removal of solvent under reduced pressure, the residue was dissolved in dichloromethane and washed with sodium thiosulphate solution (2 x 20 mL) and water (10 mL). The organic layer was dried and concentrated under vacuum to give 3.35 g of brown oil. This crude product **15** was used in the next step without further purification.

To a suspension of sodium hydride (60% dispersion in mineral oil, 1.23 g, 31 mmol) in DMF (5 mL) in an ice bath, N-hydroxyphthalimide (4.9 g, 31 mmol) in DMF (5 mL) was added over a period of 10 min. The mixture was stirred for further 30 min at room temperature. Then a solution of crude product **15** in DMF was added to the mixture. The reaction was stirred overnight. DMF was evaporated under reduced pressure. To the residue was added saturated ammonium chloride solution (50 mL) and extracted with ether (3 x 30 mL). The organic layer was separated and further washed with water (20 mL), brine (2 x 20 mL) and dried over anhydrous sodium sulphate. Solvent was removed under reduced pressure. Purification by flash column chromatography provided 5.23 g of compound **16** (18 mmol, yield 61%) as a white solid : ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 4.72 (s, 2H), 7.85 (m, 4H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 166.0, 163.1, 134.6, 128.9, 123.6, 83.0, 73.4, 28.0; HRMS for $C_{14}H_{15}O_5N$ (M^+), calcd 277.0950, found 277.0951.

Preparation of Compounds 17 and 18

To compound **16** (1.77 g, 6.38 mmol) in 15 mL of methanol was added, hydrazine hydrate (1.28 mL, 25.6 mmol) was added. The mixture was stirred at room temperature for 15 min and concentrated under vacuum. The residue was dissolved in 3% sodium carbonate solution (10 mL) and extracted with diethyl ether (2 x 20 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the crude product **17** which was used in the next step without further purification.

To a vigorously stirred solution of compound **17** in 5 mL of 6% sodium bicarbonate solution and 5 mL of dichlormethane, 0.54 mL of pivaloyl chloride (6.39 mmol) was added dropwise in an ice bath. The reaction mixture was stirred overnight. The organic layer was separated out and washed with water (10 mL). After removal of solvent, 0.93 g of compound **18** (4.34 mmol, yield 68%) was obtained as a white solid.: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, H), 1.50 (s, 9H), 4.36 (s, 2H), 9.13 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 175.6, 169.3, 82.8, 72.3, 38.0, 28.1, 27.1; CIMS *m/z* 232 (M^++1).

Preparation of Acid 19

To comopund **18** (0.89 g, 4.13 mmol) dissolved in 5 mL of dichloromethane in an ice

bath, 5 mL of trifluoroacetic acid was added. The reaction was then stirred at room temperature for 2 h and concentrated to dryness. Then 10 mL of 6% sodium bicarbonate solution was added to dissolve the residue, then washed with dichloromethane (2 x 5 mL). The aqueous layer was acidified with dilute hydrochloric acid and extraced with ethyl acetate (2 x 15 mL). The organic layer was concentrated under reduced pressure to provide 0.62 g of acid **18** (3.92 mmol, yield 95%): ^{1}H NMR (300 MHz, CD_3CN) δ 1.17 (s, 9H), 4.47 (s, 2H), 10.12 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 180.3, 170.9, 76.2, 37.9, 26.6; CIMS *m*/Z 176 (M^++1).

Preparation of Acid Chloride 20

To a solution of acid **19** (0.62 g, 3.92 mmol) in 10 mL of dichloromethane was added 0.68 mL of oxalyl chloride (7.8 mmol), followed by 2 drops of DMF. The reaction was stirred until no further gas evolution was noticed. The solution was concentrated under reduced pressure and azeotroped with toluene to provide acid chloride **20** which was used in the preparation of diamide **10**, **11**, **12** without further purification.

Preparaton and Characterization of Diamide 10

The acid chloride **20** was stirred with of pyridine (0.37 mL, 4.28 mmol) in dichloromethane in an ice bath and diethylamine (0.89 mL, 8.53 mmol) was added in dropwise. The reaction was stirred for 4 h. After removal of solvent, purification by flash column column chromatography provided 0.56 g of compound 10 (2.42 mmol, yield 62%) as a brown oil.: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (m, 15 H), 3.19 (q, J = 7.2 Hz, 2H), 3.4 (q, J =7.1 Hz, 2H), 4.58 (s, 2H), 9.82 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 175.6, 168.0, 72.0, 41.1, 40.3, 37.9, 27.1, 14.1, 12.9; IR (CH_2Cl_2) 3400 cm^{-1}; CIMS *m*/Z 231 (M^++1), HRMS for $C_{11}H_{22}N_2O_3$ (M^+), calcd 230.1630, found 230.1628.

Preparation and Charaterization of Diamide 11

The acid chloride **20** was stirred with pyridine (0.74 mL, 8.58 mmol) in dichloromethane in an ice bath and of O-methyl hydroxylamine hydrochloride (0.71 g, 8.58 mmol) was added in. The reaction mixture was stirred under nitrogen for 4 h. After removal of solvent under vacuum, purification by flash column chromatography provided 0.46 g of compound **11** (2.26 mmol, yield 58%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 9H), 3.80 (s, 3H), 4.43 (s, 2H), 8.83 (s, 1H), 11.5 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 178.0, 165.9, 75.7, 64.2, 38.1, 27.0; IR (CH_2Cl_2) 3386, 3200 cm^{-1}; CIMS *m*/Z 205 (M^++1), HRMS for $C_8H_{16}N_2O_4$ (M^+), calcd 204.1110, found 204.1103.

Preparation and Characterization of Diamide 12

The acid chloride **20** was stirred with pyridine (0.74 mL, 8.58 mmol) in dichloromethane (5 mL) in an ice bath and isobutylamine (0.78 mL, 7.8 mmol) was added in

dropwise. The reaction mixture was stirred under nitrogen for 4 h. After removal of solvent under vacuum, purification by flash column chromatography provided 0.538 g of pure compound **12** as a white solid (2.34 mmol, 60% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.7 Hz, 6H), 1.21 (s, 9H), 1.83 (m, 1H), 3.12 (t, J = 6.3 Hz, 2H), 4.35 (s, 2H), 8.53 (br, 1H), 9.50 (br, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 178.6, 168.7, 76.0, 46.6, 38.0, 28.4, 27.1, 20.2; IR (CH_2Cl_2) 3428, 3385, 3300 cm^{-1}; CIMS *m/z* 231 (M^++1), HRMS for $C_{11}H_{22}N_2O_3$ (M^+), calcd 230.1630, found 230.1630.

Preparation and Characterization of Tripeptide 13

To a suspension of *N*-Cbz-*L*-Valine (1.63 g, 6.5 mmol) and compound **17** (0.6 g, 5.42 mmol) in dichloromethane (10 mL), 1.32 g of 1-hydroxy-benzotriazole (9.75 mmol) was added, followed by 2.90 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide (9.75 mmol). The reaction mixture was stirred under nitrogen overnight. The organic layer was separated out and washed with 6% sodium bicarbonate solution and brine. After removal of solvent under vacuum, purification by flash column chromatography provided 1.54 g of compound **21** (4.65 mmol, yield 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.34 (m, 5H), 5.43 (s, 1H), 5.11 (s, 2H), 4.37 (s, 2H), 3.87 (m, 1H), 2.06 (m, 1H), 1.48 (s, 9H), 0.94 (d, J = 6.6 Hz, 6H).

To compound **21** (1.54 g, 4.065 mmol) dissolved in 10 mL of dichloromethane in an ice bath, was added 10 mL of trifluroacetic acid. The reaction was then stirred at room temperature for 2 h and concentrated to dryness. The residue was dissolved in 15 mL of 6% sodium bicarbonate solution, then washed with dichloromethane (2 x 5 mL). The aqueous layer was acidified with dilute hydrochloric acid and extracted with ethyl acetate (3 x 25 mL). The organic layer was dried and concentrated under reduced pressure to provide 1.26 g of acid **22** (3.90 mmol, yield 96%).

The acid **22** was dissolved in 10 mL of CH_2Cl_2, then 0.65 g of *L*-Alanine methyl ester hydrochloride (4.68 mmol) and 1.30 mL of triethylamine (9.36 mmol) were added. The salt was dissolved and 1.05 g of 1-hydroxy-benzotriazole (7.8 mmol) was added, followed by 1.53 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide (5.15 mmol). The reaction mixture was stirred under nitrogen overnight. The organic layer was separated out and washed with 6% sodium bicarbonate solution and brine. After removal of solvent under vacuum, purification by flash column chromatography provided 1.31 g of tripeptide **13** as white solid (3.20 mmol, yield 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.42 (d, J = 7.41Hz, 1H), 7.35 (m, 5H), 5.56 (d, J = 9 Hz, 1H), 5.12 (d, J = 12.1 Hz, 1H), 5.03 (d, J = 12.2 Hz, 1H), 4.60 (m, 1H), 4.37 (d, J = 3.32 Hz, 2H), 3.85 (m, 1H), 3.71 (s, 3H), 2.11 (m, 1H), 1.44 (d, J = 7.3 Hz, 3H), 0.96 (d, J = 4.13 Hz, 3H), 0.94 (d, J = 4.1 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 173.1, 170.8, 168.1, 156.7, 135.8, 128.6, 128.4, 128.0, 75.8, 67.4, 58.2, 52.5, 47.8, 30.4, 19.1, 18.2, 17.6; FABMS(+ve) 410 (M^++1).

^{1}H NMR dilution experiments were carried out on a Bruker–300 DPX multinuclear FT–NMR spectrometer. IR experiments were carried out on a Perkin Elmer 1600 FT–IR spectrometer or a Bio–Rad FT–155 spectrometer.

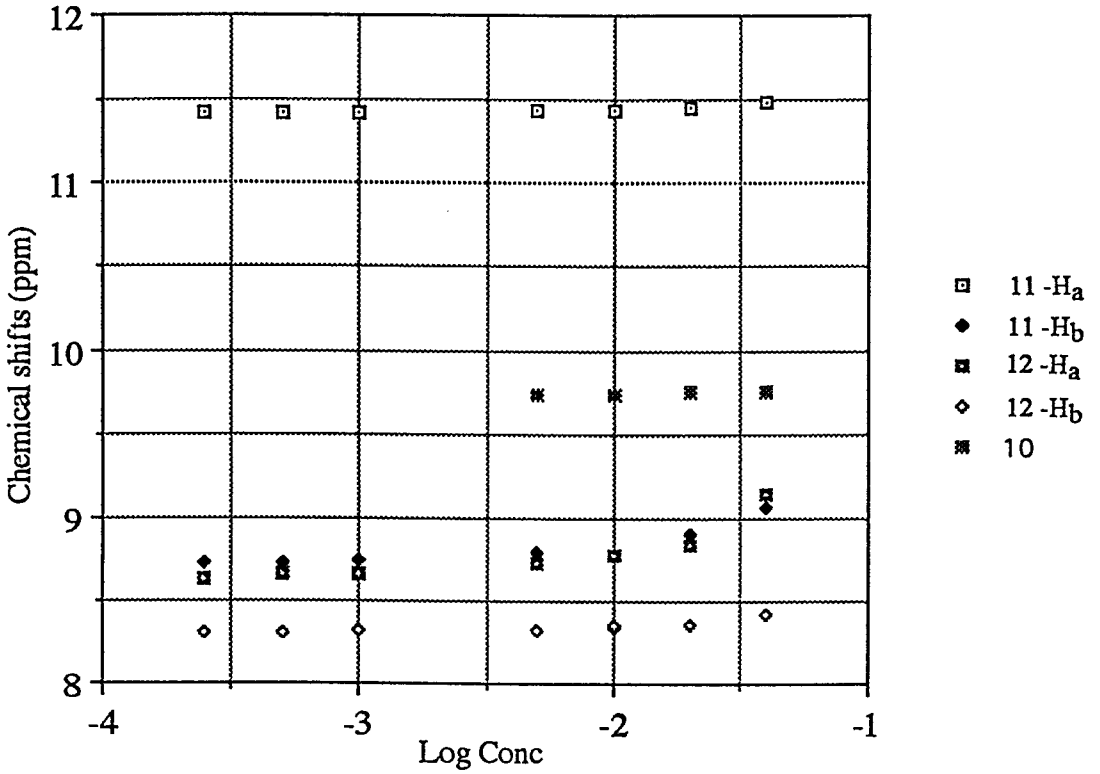
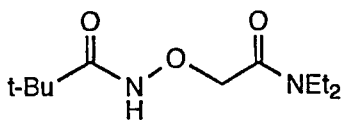


Figure 1. ^{1}H NMR chemical shifts of amide protons of compounds **10–12** in CD_2Cl_2 at 25 °C as a function of the logarithm of concentration



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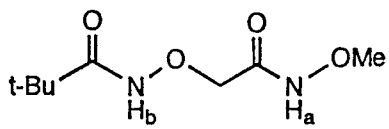

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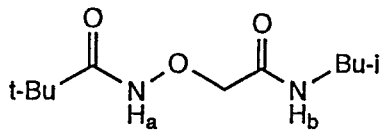

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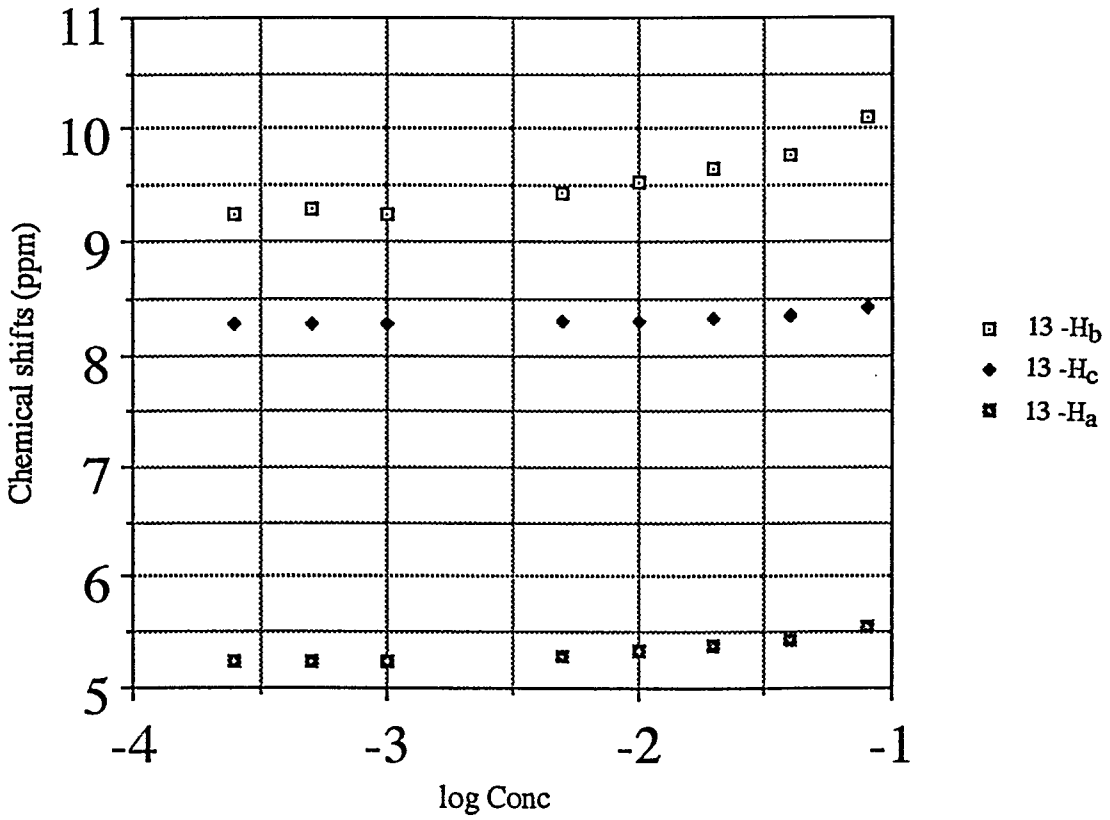
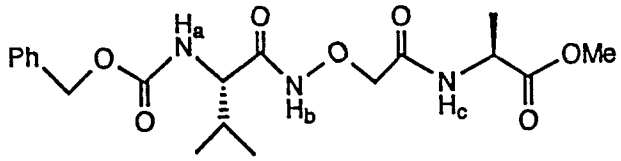


Figure 2. ^{1}H NMR chemical shifts of amide protons of compound **13** in CD_2Cl_2 at 25 °C as a function of the logarithm of concentration



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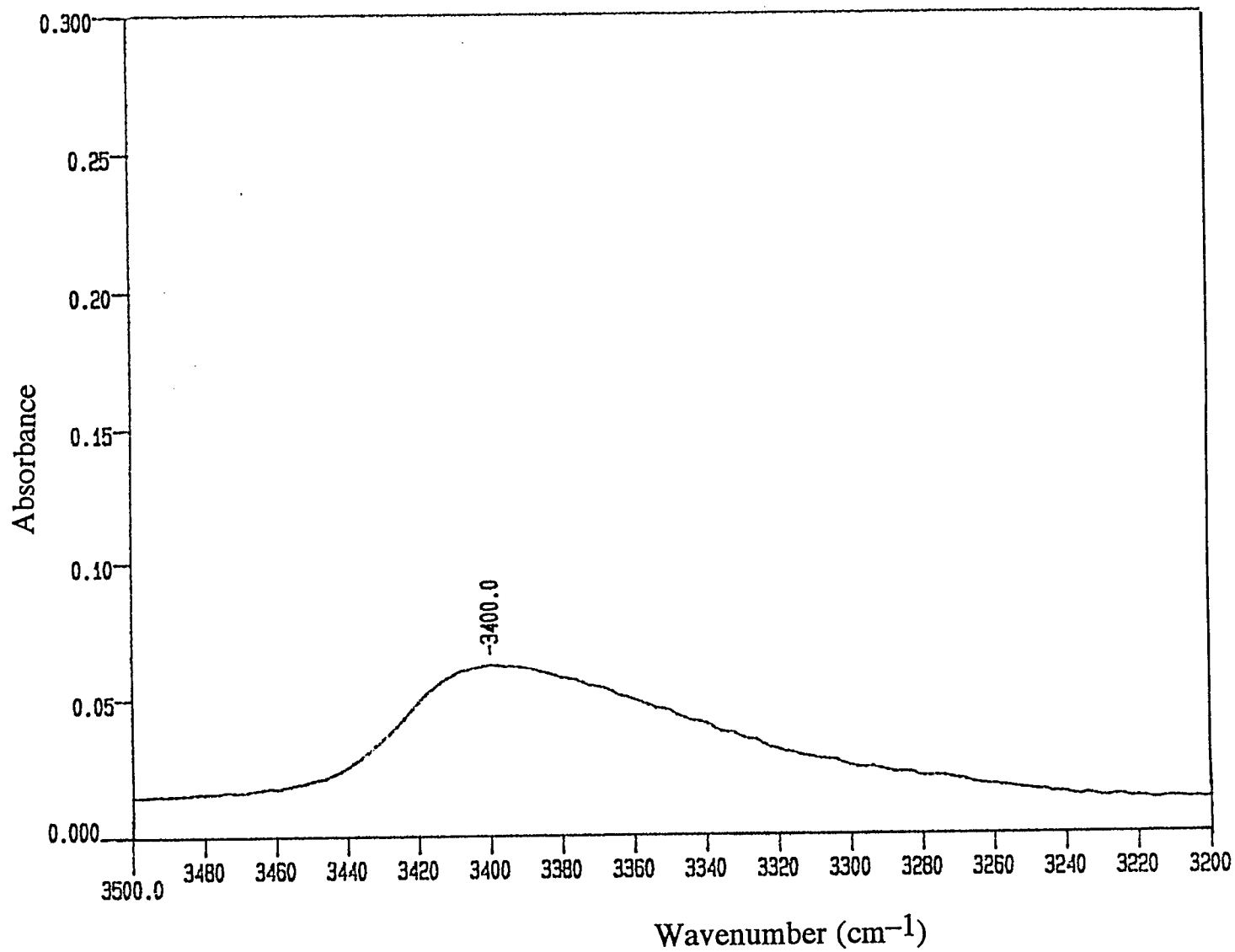

Figure 3. FTIR spectra for the N–H stretch region of **10** in CH_2Cl_2 solution at room temperature after subtraction of the spectrum of pure CH_2Cl_2 (5 mM)

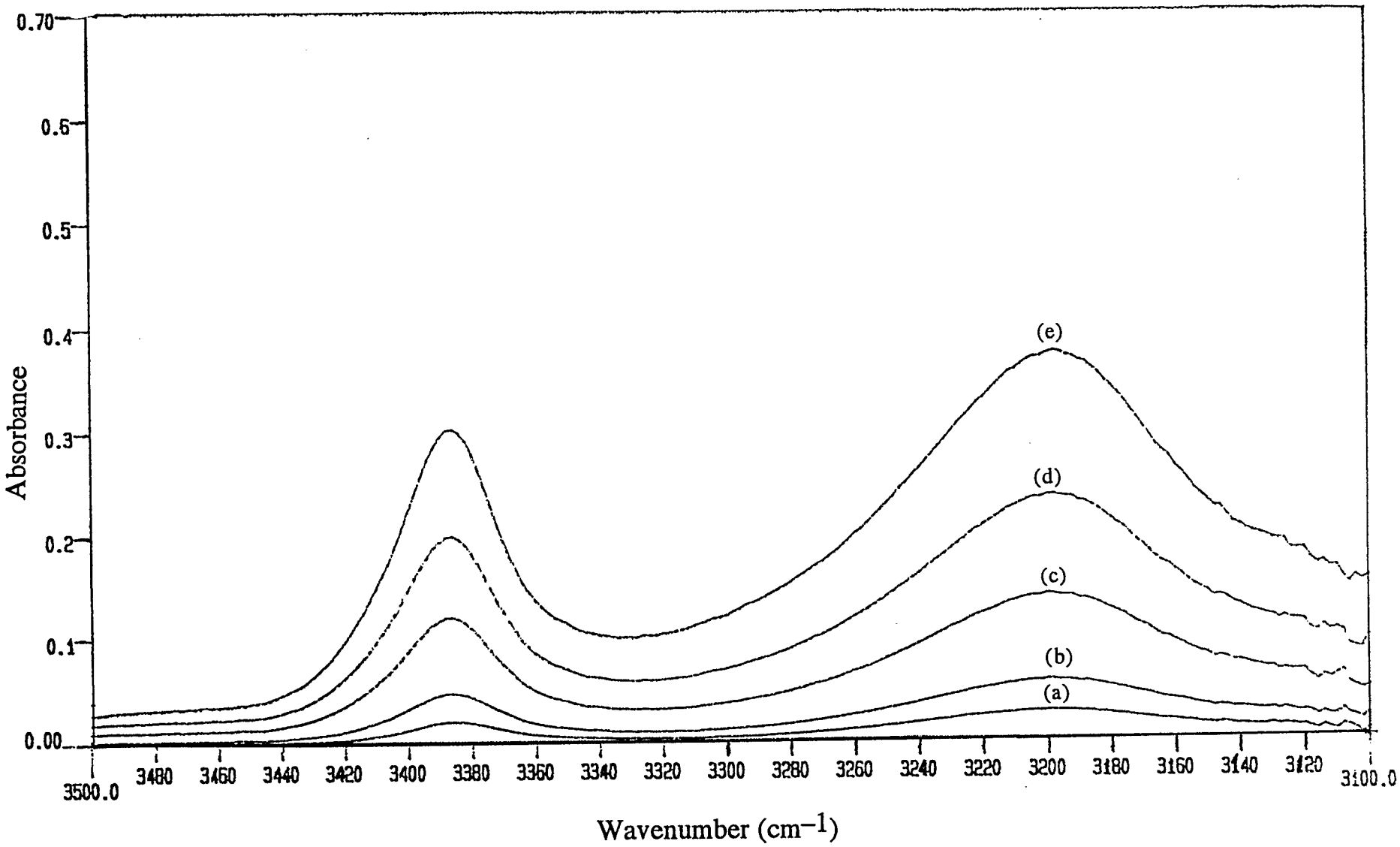

Figure 4. FTIR spectra for the N–H stretch region of **11** in CH_2Cl_2 solution at room temperature after subtraction of the spectrum of pure CH_2Cl_2: (a) 0.5, (b) 1, (c) 5, (d) 10, (e) 20 mM

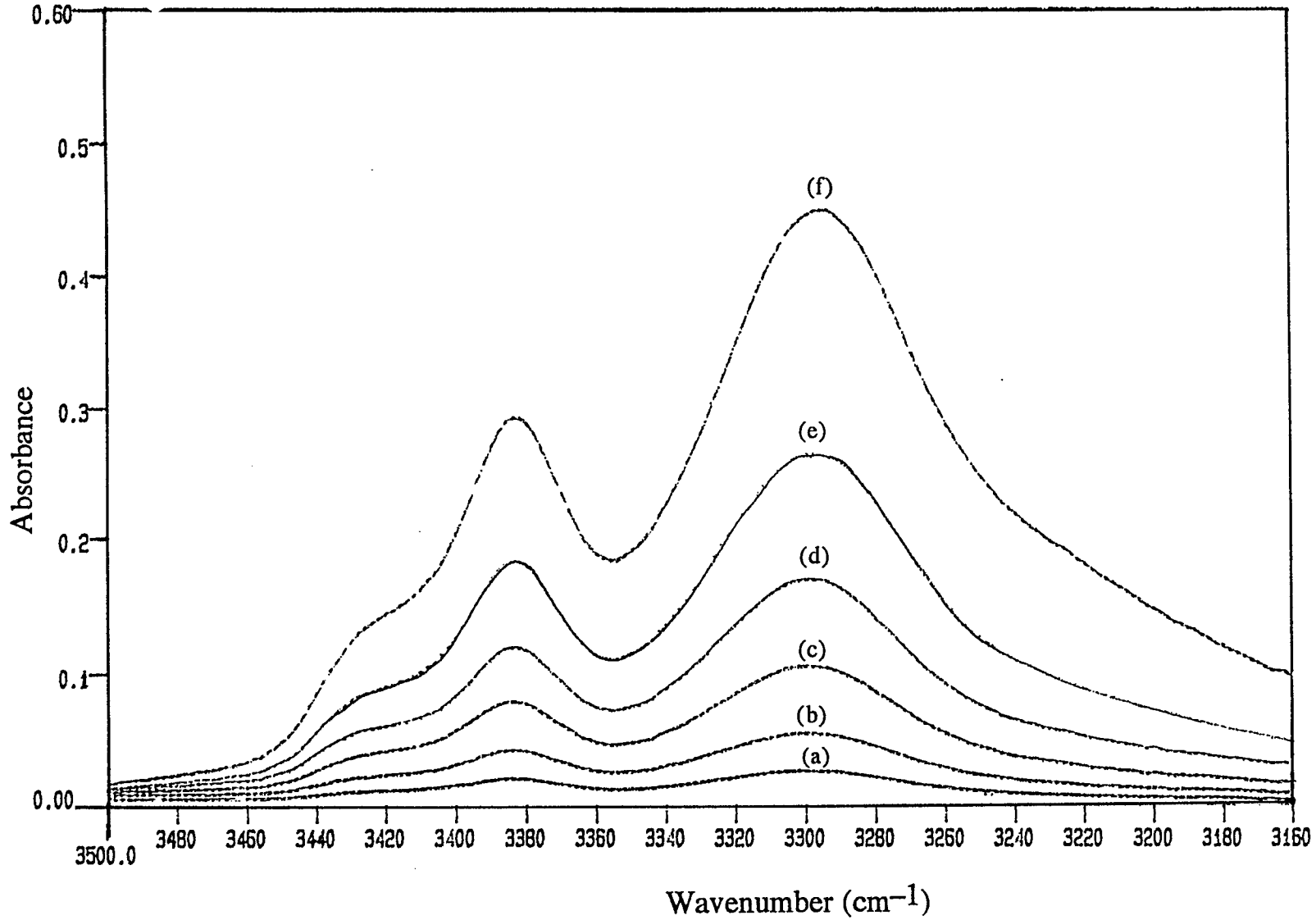

Figure 5. FTIR spectra for the N–H stretch region of **12** in CH_2Cl_2 solution at room temperature after subtraction of the spectrum of pure CH_2Cl_2: (a) 0.5, (b) 1, (c) 5, (d) 10, (e) 20, (f) 40 mM, after subtraction of the spectrum of pure CH_2Cl_2

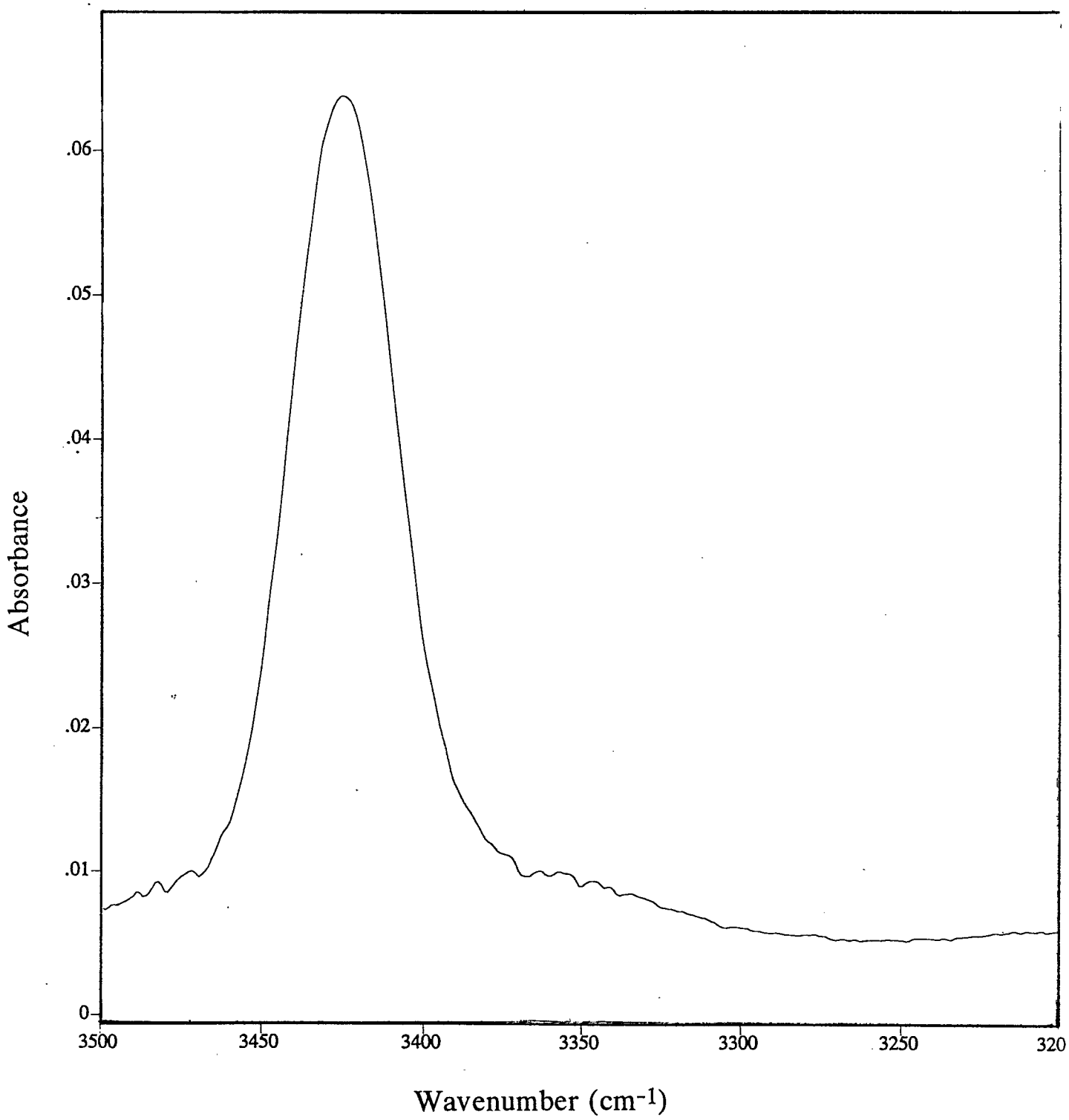

Figure 6: FTIR spectra for N–H stretch region of *N*-Cbz-Val-Ala-OMe (5mM) in CH_2Cl_2 at room temperature after subtraction of the spectrum of pure CH_2Cl_2

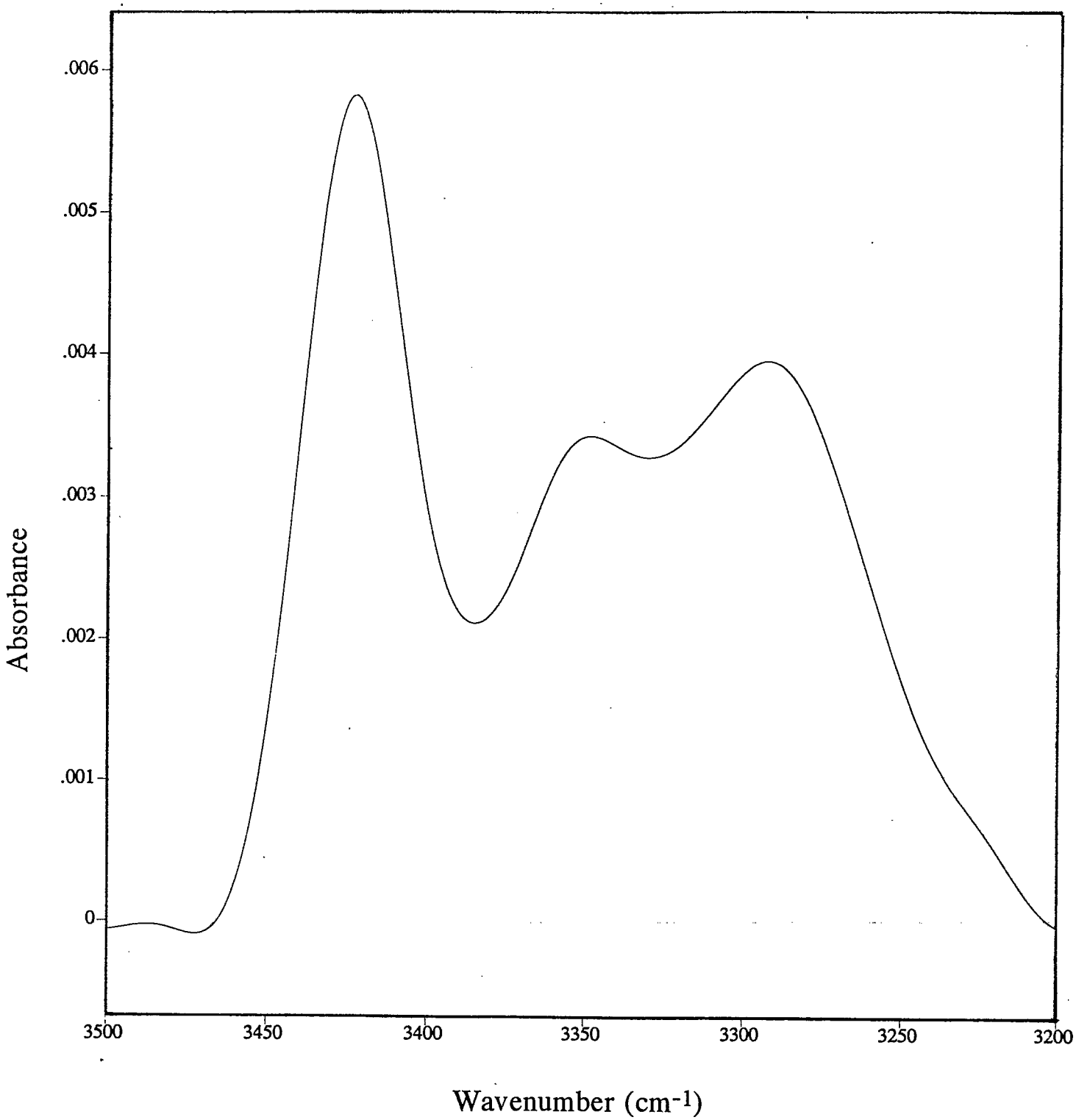

Figure 7: FTIR spectra for N–H stretch region of compound **13** (0.5 mM) in CH_2Cl_2 at room temperature after subtraction of the spectrum of pure CH_2Cl_2

The cartesian coordinates of structure 5 (HF/6-31G*)

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	1.187624	0.375101	0.286039
2	6	-0.318124	0.571072	0.113107
3	7	-1.010718	-0.565004	-0.182752
4	8	-2.278448	-0.397414	-0.666146
5	8	-0.830716	1.629403	0.321769
6	1	-0.526345	-1.283093	0.672966
7	6	-3.236190	-0.531511	0.355007
8	1	-4.196291	-0.410360	-0.126613
9	1	-3.105031	0.235512	1.105889
10	1	-3.175294	-1.512937	0.812193
11	6	1.949204	1.538464	-0.338458
12	1	3.012001	1.447132	-0.145455
13	1	1.601259	2.475242	0.073647
14	1	1.795624	1.550713	-1.411648
15	8	1.554898	-0.859080	-0.270313
16	6	2.704851	-1.454310	0.256944
17	1	2.821887	-2.410424	-0.233018
18	1	2.606248	-1.614499	1.327533
19	1	3.590647	-0.856106	0.070725
20	1	1.360269	0.357689	1.360654

The cartesian coordinates of structure 6 (HF/6-31G*)

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	-1.258355	0.360352	-0.219861
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3	7	1.082894	-0.247541	-0.332378
4	8	2.410737	0.084723	-0.174916
5	8	0.512882	1.943298	-0.338439
6	1	0.804286	-1.097576	0.106334
7	6	3.119922	-0.942111	0.449952
8	1	4.142253	-0.601217	0.513929
9	1	3.083555	-1.858948	-0.132396
10	1	2.740721	-1.132470	1.451077
11	6	-2.059929	1.288888	0.683052
12	1	-3.112957	1.032331	0.656052
13	1	-1.943655	2.313909	0.360530
14	1	-1.712891	1.204852	1.706754
15	8	-1.328132	-0.977042	0.204835
16	6	-2.436137	-1.705065	-0.240071
17	1	-2.331427	-2.710996	0.141204
18	1	-2.470680	-1.739144	-1.325771
19	1	-3.367017	-1.287476	0.129038
20	1	-1.621286	0.436757	-1.242953

The cartesian coordinates of structure 8 (HF/6-31G*)

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	3.105858	0.014852	0.733813
2	6	1.799651	0.198812	-0.002229
3	7	0.947121	-0.877171	0.109555
4	8	-0.035856	-0.956302	-0.842546
5	8	1.520937	1.194937	-0.596909
6	1	1.387332	-1.767976	0.215788
7	6	-1.316541	-1.101737	-0.275851
8	6	-1.991309	0.181110	0.185444
9	1	-1.930277	-1.525067	-1.059611
10	1	-1.296170	-1.789306	0.557719
11	1	3.016600	-0.666420	1.571447
12	1	3.845712	-0.377658	0.043081
13	1	3.444896	0.979227	1.083169
14	8	-2.989386	0.093010	0.848648
15	7	-1.459770	1.332398	-0.244520
16	1	-0.558492	1.372688	-0.670888
17	1	-1.872578	2.176539	0.083445

The cartesian coordinates of structure 9 (HF/6-31G*)

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
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3	7	-0.806390	0.314816	-0.195780
4	8	-0.024030	-0.595974	-0.849310
5	8	-2.403170	-1.241828	0.163891
6	1	-0.657701	1.227279	-0.569153
7	6	1.083883	-0.945497	-0.088366
8	6	2.082920	0.200486	0.013336
9	1	0.787119	-1.268329	0.903431
10	1	1.543587	-1.781936	-0.601210
11	1	-2.502866	1.923206	0.788615
12	1	-3.545819	1.323485	-0.496960
13	1	-3.749311	0.716397	1.138625
14	8	1.885184	1.274951	-0.476701
15	7	3.200573	-0.095587	0.714395
16	1	3.395259	-1.008383	1.055148
17	1	3.916583	0.592840	0.776297